Original Article

Cardiovascular Risk Factor Profiles and Endothelial Function in Coronary Artery Disease Patients Treated with Statins

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Although endothelial dysfunction is associated with cardiovascular risk factors and is improved by cholesterol-lowering therapy, the relationship between endothelial function and cardiovascular risk factor profiles has not been fully investigated in coronary artery disease patients who have been treated with statins. We investigated endothelial function in male hypercholesterolemic patients ($n = 53$) who underwent statin therapy over 6 months in a cross-sectional study. Patients were classified into three groups based on the results of coronary angiography: a normal coronary artery group ($n = 15$), an angina pectoris group ($n = 20$) and a myocardial infarction group ($n = 18$). Endothelial function was assessed by measuring flow-mediated dilatation after reactive hyperemia in the brachial artery, and serum lipid, lipoprotein (a), glucose and insulin levels were measured. Significant associations were observed between the status of coronary disease and systolic blood pressure, lipoprotein (a), glucose and insulin levels ($p < 0.05$, respectively), and the levels of these risk factors in the myocardial infarction group were higher than those in the other groups. Flow-mediated dilatation was also associated with the status of coronary disease ($p < 0.05$), and the myocardial infarction group showed the lowest levels of flow-mediated dilatation ($p < 0.05$). Flow-mediated dilatation was negatively correlated with systolic and diastolic blood pressures, serum levels of lipoprotein (a), glucose and insulin, and the status of coronary disease. Stepwise multiple regression analysis also revealed that lipoprotein (a), diastolic blood pressure and the status of myocardial infarction were significantly correlated with impaired vasodilatation. Serum lipids, age and smoking habit were independent of flow-mediated dilatation. In conclusion, even after cholesterol-lowering treatment, male patients with myocardial infarction still had endothelial dysfunction, and higher levels of lipoprotein (a) may be associated with endothelial dysfunction in such patients. (*Hypertens Res* 2004; 27: 723–729)

Key Words: coronary artery disease, endothelium, hypercholesterolemia, insulin, lipoprotein (a)

Introduction

Impaired endothelial function has been shown to be associated with risk factors for coronary artery disease (CAD), including hypercholesterolemia (1, 2). Endothelial dysfunction

has been reported to be involved not only in the early features of atherogenesis (3), but also in the progression of CAD (4). Endothelial dysfunction also precedes and predicts clinical cardiovascular disease in human atherogenesis (5) and should be considered as a target of therapy (6). Although previous reports have shown that hypercholesterolemia is

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one of the strongest determinants of endothelial dysfunction and that statin treatment improved impaired endothelial function (7, 8), long-term statin treatment did not significantly affect coronary endothelial vasomotor function in CAD patients (9). In high-risk CAD patients who are receiving statin treatment, the effects of lower cholesterol levels on endothelial function are more complex than previously thought (9), and endothelial function after statin treatment has not been fully investigated in CAD patients.

Previous studies have demonstrated that several atherosclerotic factors are closely related to endothelial dysfunction, such as hypertension, diabetes, aging and smoking habit (10–14). Lipoprotein (a) (Lp(a)) is also related to impaired endothelium-dependent dilatation (15, 16), and is an independent risk factor for atherogenic disease (17–19). Although some studies have reported an association between endothelial function and Lp(a), this has mainly been seen in non-CAD patients with hypercholesterolemia (15, 16). Hyperinsulinemia and hyperglycemia are also involved in the impairment of endothelial function (20, 21); however, no data are available regarding the association between endothelial function and serum levels of glucose and insulin in hypercholesterolemic patients treated with statins.

In the present study, we examined the association between endothelial function and CAD risk factors including Lp(a), glucose and insulin in male CAD patients who had been receiving statins.

Methods

Study Population

Fifty-three male hypercholesterolemic patients (WHO type IIa, $n = 30$, type IIb, $n = 23$) who had been treated with statins for at least 6 months participated in this study. The statins used were atorvastatin ($n = 11$), fluvastatin ($n = 5$), simvastatin ($n = 15$), and pravastatin ($n = 22$). All of the patients underwent coronary angiography and were grouped according to the status of coronary disease: normal coronary artery group ($n = 15$), angina pectoris (AP) group ($n = 20$), and myocardial infarction (MI) group ($n = 18$). Normal coronary artery cases were defined as those who had normal coronary arteries ($<25\%$ stenosis) as proven by coronary angiography and who had no clinical evidence of CAD in their history or on exercise ECG. Patients with AP were defined as those who had clinical symptoms of CAD or positive exercise ECG and more than 90% coronary stenosis (significant stenosis) as proven by coronary angiography. Patients with old MI were those in whom MI was diagnosed based on symptoms, ECG, and serum creatine kinase isoenzyme of more than twice the upper level of normal. Cardiac catheterization analysis including coronary angiography and left ventriculography were performed in the acute phase, and a definitive diagnosis of MI was made. Patients with recent MI (within 6 months of onset), heart failure, hepatic or renal dis-

ease, insulin-dependent diabetes mellitus or cerebrovascular disease were excluded from the study. After statin therapy, none of the patients suffered critical cardiac events or required interventional revascularization or cardiac bypass surgery.

Data were collected regarding weight and height to calculate the body mass index (BMI), systolic and diastolic blood pressures (SBP/DBP), and the administration of angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, calcium-channel blockers, nitrates, β -blockers, diuretics, aspirin and non-steroidal anti-inflammatory agents. Smokers were defined as those having a history of at least 2 pack-years of cigarette smoking before the study. All current smokers refrained from smoking more than 4 h before the examination. The study was approved by the ethics committee of Fukuoka University Hospital and all of the participants gave their informed consent.

Coronary Angiography

Coronary angiography was performed using the Judkins technique. Coronary arteries were divided into 15 segments and the extent and severity of stenosis was assessed according to the AHA Committee Report. To evaluate the severity of coronary atherosclerosis, angiographic findings were assessed by two different methods: 1) counting the number of diseased vessels that showed $>90\%$ stenosis and 2) assessing the severity of stenosis by assigning points to each lesion according to the modified Jenkins' method (22) as follows: less than 25% stenosis of the luminal diameter, 0 points; 25–49% stenosis, 4 points; 50–74%, 8; 75–89%, 9; 90–99%, 10; and total occlusion, 10 points. The points for all lesions were added to obtain the coronary score.

Laboratory Assays

Peripheral blood was obtained early in the morning after more than 12 h of fasting. Total cholesterol (TC) and triglycerides (TG) were measured enzymatically. High density lipoprotein-cholesterol (HDL-C) was determined by a precipitation method. Low density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald equation. Apolipoprotein (apo) AI and apo B were determined by the turbidity immunoassay. Serum Lp(a) levels were measured by enzyme-linked immunosorbent assay (Biopool, Umea, Sweden) (23). Glucose was measured with a Hitachi 747 analyzer according to standard procedures. Insulin was measured by conventional radioimmunoassay.

Vascular Studies

Ultrasound measurement of the brachial artery was performed in the supine position at the elbow of the right arm with an ALOKA SSD-5500 ultrasound machine equipped with a 10.0-MHz linear-array transducer after 10 min of rest.

Table 1. Characteristics of the Study Patients and the Association of the Extent of Coronary Disease with Risk Factors

	Total (n = 53)	Normal coronary (n = 15)	AP (n = 20)	MI (n = 18)
Age (year)	62.9 ± 6.6	61.3 ± 5.4	62.7 ± 6.5	64.7 ± 7.7
BMI (kg/m ²)	23.1 ± 2.5	23.3 ± 2.6	22.7 ± 2.4	23.4 ± 2.6
Smoker	25 (47)	6 (40)	9 (45)	10 (56)
Pack-year	19.6 ± 23.1	17.3 ± 23.2	15.3 ± 18.5	26.4 ± 27.1
Systolic BP (mmHg)	141 ± 13	136 ± 14	141 ± 13	146 ± 12*
Diastolic BP (mmHg)	76 ± 8.8	75 ± 8.0	76 ± 9.8	75 ± 7.3
Total cholesterol (mg/dl)	178 ± 31	176 ± 33	186 ± 28	170 ± 32
Triglyceride (mg/dl)	147 ± 79	166 ± 114	140 ± 52	138 ± 71
LDL-cholesterol (mg/dl)	102 ± 23	99 ± 25	108 ± 22	96 ± 21
HDL-cholesterol (mg/dl)	47 ± 14	44 ± 14	50 ± 16	46 ± 10
LDL/HDL cholesterol	2.4 ± 0.8	2.4 ± 0.8	2.4 ± 0.9	2.2 ± 0.7
Apo AI (mg/dl)	112 ± 19	110 ± 24	116 ± 19	109 ± 14
Apo B (mg/dl)	98 ± 26	97 ± 32	102 ± 23	94 ± 25
Apo B/Apo AI	0.89 ± 0.24	0.90 ± 0.29	0.89 ± 0.20	0.87 ± 0.23
Lp(a) (mg/dl)	23.4 ± 24.6	18.7 ± 11.6	20.4 ± 14.6	30.6 ± 14.7*,†
Median [range]	19 [3–60]	19 [3–42]	16 [5–52]	26 [12–60]
Glucose (mg/dl)	100 ± 29	87 ± 10	97 ± 28	113 ± 35*
Insulin (μU/ml)	10.5 ± 9.4	6.3 ± 3.3	9.7 ± 11.0	14.8 ± 9.6*
ACE inhibitor	12 (23)	1 (7)	8 (40)	3 (17)
ARB	17 (32)	2 (13)	6 (30)	9 (50)*

Unless otherwise indicated, data presented are mean ± SD or number (%) of patients. * $p < 0.05$ vs. the normal coronary group.

† $p < 0.05$ vs. the AP group. AP, angina pectoris; MI, myocardial infarction; BMI, body mass index; BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; Apo, apolipoprotein; Lp(a), lipoprotein (a); ACE, angiotensin-converting enzyme; ARB, angiotensin II type 1 receptor blocker.

Imaging of the brachial artery was performed longitudinally, with the center of the artery identified by the clearest visualization of the anterior and posterior intimal layers. After a satisfactory transducer position was found, the skin was marked and the arm was maintained in that position throughout the study. A baseline measurement of brachial artery diameter was made in the center of the artery.

Endothelium-dependent vasodilatation (flow-mediated dilatation, FMD) was assessed by measuring the change in the diameter of the brachial artery after 60 s of reactive hyperemia relative to baseline measurements after deflation of a cuff on the forearm inflated to 250 mmHg for 5 min, a response which has previously been shown to be mediated primarily by nitric oxide (24). After baseline conditions were reestablished 10 min later, the arterial diameter was measured again, followed by administration of 0.4 mg of sublingual nitroglycerin spray to assess endothelium-independent vasodilatation. Three min later, the arterial diameter was measured again. All images were coded and recorded on S-VHS videotape for subsequent blinded analysis. Arterial diameter was measured in mm as the distance between the an-

terior wall media-adventitial interface and the posterior wall intima-lumen interface at end-diastole at two sites along the artery and for three cardiac cycles, with these six measurements averaged (25). All measurements were performed by two physicians (Y.O. and M.T.). Within-subject variability was assessed from all six scans from 10 control subjects. The mean FMD and within-subject SD were 6.53 ± 2.2 , resulting in a coefficient of variation of 33.7% (26). The number of subjects needed to detect a difference in group changes with a probability of 0.05 was 14 per group in this cross-sectional study for comparison of group changes (26), and, according to these results, the number of patients in the present study had 80% power at the 5% level.

Statistical Analysis

All data are expressed as the mean ± SD, unless stated otherwise. Statistical analysis was performed using an SAS software package (Statistical Analysis System, Version 6.12; SAS Institute Inc., Cary, USA). Categorical variables (such as smoking) among the coronary disease groups (normal, AP

Table 2. The Association of the Group of Coronary Disease with Endothelium-Dependent and -Independent Vasodilation Parameters

	Normal coronary (<i>n</i> = 15)	AP (<i>n</i> = 20)	MI (<i>n</i> = 18)
Diameter (control 1) (mm)	5.07 ± 0.61	4.73 ± 0.49	4.76 ± 0.58
Diameter (RH) (mm)	5.41 ± 0.62	5.01 ± 0.52	4.92 ± 0.58*
FMD (%)	6.79 ± 2.69	5.85 ± 3.25	3.45 ± 1.39* [†]
Diameter (control 2) (mm)	5.13 ± 0.52	4.83 ± 0.46	4.82 ± 0.45
Diameter (NTG) (mm)	5.50 ± 0.51	5.23 ± 0.49	5.14 ± 0.43
NTG-induced dilatation (%)	7.28 ± 2.48	8.25 ± 3.68	6.67 ± 3.25
Number of diseased vessels	0.0 ± 0.0	1.35 ± 0.49*	1.29 ± 0.47*
Coronary score	0.0 ± 0.0	21.2 ± 7.9*	21.0 ± 7.3*

Data presented are mean ± SD. * $p < 0.05$ vs. the normal coronary group. [†] $p < 0.05$ vs. the AP group. AP, angina pectoris; MI, myocardial infarction; RH, reactive hyperemia; FMD, flow mediated dilatation; NTG, nitroglycerin.

and MI) were compared by a χ^2 analysis. Differences in continuous variables among the groups were examined by an analysis of variance (ANOVA). Echo study parameters were compared by ANOVA and also by an analysis of covariance after adjusting for age and conventional risk factors. Associations between risk factors and echo study parameters were analyzed by a simple regression analysis. The magnitude of the correlation between multivariates and FMD was analyzed by a multiple stepwise linear regression analysis (entry criteria, $F = 5$). Differences with a p value of less than 0.05 were considered statistically significant.

Results

The characteristics of the patients are summarized in Table 1. Twenty-five were smokers. The mean LDL-C level was 102 ± 23 mg/dl and only 4 patients (7.5%) showed an LDL-C level over 130 mg/dl.

Table 1 compares the risk factors in subjects grouped according to the status of coronary disease. There was no association between the status of coronary disease and age, BMI, smoking habit, DBP, serum lipids or apolipoproteins. Significant associations were observed between the status of coronary disease and SBP, Lp(a), glucose and insulin levels, and the MI group showed higher levels of these parameters than the other groups ($p < 0.05$, respectively, Table 1). The percentage of patients who were taking angiotensin II type I receptor antagonists in the MI group was significantly higher than that in the normal coronary artery group ($p < 0.05$, Table 1), while there were no significant differences in the percentage of those taking angiotensin-converting enzyme inhibitors, calcium-channel blockers, nitrates, β -blockers, diuretics, aspirin or non-steroidal anti-inflammatory agents among the three groups.

The endothelium-dependent parameter FMD was significantly lower in the MI group than in the normal coronary

artery and AP groups ($p < 0.05$, respectively, Table 2), while no significant difference was observed in nitroglycerin-induced vasodilatation, which reflects endothelium-independent dilatation, among the three groups (Table 2). The MI group also showed a significantly lower FMD than the normal coronary artery and AP groups after adjusting for age and smoking habit by an analysis of covariance. Indices of the severity of coronary atherosclerosis, i.e., the number of diseased vessels and coronary score, were significantly higher in the AP and MI groups than in the normal coronary artery group, while there were no significant differences in these indices of the severity of coronary atherosclerosis between the AP and MI groups (Table 2). FMD was also associated with the status of coronary disease ($p < 0.05$) after adjusting for the administration of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists by an analysis of covariance.

FMD was negatively correlated with SBP and DBP, serum levels of Lp(a), glucose and insulin, and the status of coronary disease AP or MI (Table 3). On the other hand, neither the levels of the other lipids nor other conventional risk factors (age, BMI or smoking) were correlated with FMD. Stepwise multiple regression analysis using these lipid components as independent values revealed that only the Lp(a) level was significantly correlated with impaired FMD ($p = 0.03$; Multivariate analysis 1 in Table 3). When the status of MI as an independent variable was considered instead of the status of coronary disease (AP or MI), DBP and the status of MI correlated with impaired FMD ($p = 0.0002$; Multivariate analysis 2 in Table 3). Associations with other conventional risk factors, including age, BMI and smoking habit, were not significant.

Discussion

Endothelium-dependent vasodilatation as assessed by ultra-

Table 3. Univariate and Multivariate Analysis of Correlation between Endothelial Function and Risk Factors

Flow-mediated dilatation	Univariate analysis		Multivariate analysis 1			Multivariate analysis 2		
	<i>r</i>	<i>p</i> value	Standardized coefficient	<i>F</i> value	<i>p</i> value	Standardized coefficient	<i>F</i> value	<i>p</i> value
LDL-cholesterol	0.172	NS	0.243	2.835	NS	0.085	0.324	NS
HDL-cholesterol	0.027	NS	0.040	0.074	NS	0.104	0.478	NS
Triglyceride	0.034	NS	0.123	0.688	NS	- 0.010	0.005	NS
Lp(a)	- 0.358	0.009	- 0.319	5.200	0.03	- 0.072	0.231	NS
Glucose	- 0.315	0.02	- 0.224	2.368	NS	- 0.071	0.225	NS
Insulin	- 0.320	0.02	- 0.231	2.541	NS	- 0.153	1.057	NS
Age	- 0.091	NS	- 0.101	0.460	NS	0.330	0.048	NS
BMI	- 0.076	NS	- 0.060	0.162	NS	- 0.106	0.497	NS
Systolic BP	- 0.363	0.008	- 0.216	2.210	NS	0.029	0.037	NS
Diastolic BP	- 0.350	0.01	- 0.229	2.484	NS	- 0.353	8.115	0.0002
Smoking*	- 0.038	NS	- 0.104	0.495	NS	- 0.082	0.294	NS
ACE inhibitors*	- 0.003	NS	0.020	0.017	NS	- 0.007	0.002	NS
Angiotensin II antagonists*	- 0.120	NS	0.037	0.062	NS	0.145	0.939	NS
Calcium-channel blockers*	- 0.111	NS	0.194	1.766	NS	0.121	0.650	NS
CAD1*	- 0.326	0.02	- 0.242	2.804	NS			
CAD2*	- 0.463	0.0005				- 0.483	15.173	0.0002

* Each categorical variable was defined smoking (+) = 1 and (-) = 0; ACE inhibitors (+) = 1 and (-) = 0; angiotensin II antagonists (+) = 1 and (-) = 0; calcium-channel blockers (+) = 1 and (-) = 0; CAD1, normal coronary = 0, AP or MI = 1; CAD2, normal coronary or AP = 0, MI = 1. NS, not significant; LDL, low density lipoprotein; HDL, high density lipoprotein; Lp(a), lipoprotein (a); BMI, body mass index; BP, blood pressure; ACE, angiotensin-converting enzyme; CAD, coronary artery disease.

sonography is primarily mediated by intrinsic nitric oxide synthesis (24). Previous reports have shown that hypercholesterolemic subjects have an impaired endothelial function due to enhanced nitric oxide inactivation by increased superoxide production (7, 27). A recent study demonstrated that the administration of statin improves endothelial dysfunction independent of any cholesterol-lowering effects (8). Statins *per se* could enhance the bioavailability of nitric oxide by directly upregulating endothelial nitric oxide synthase expression (28) and by preventing nitric oxide degradation by free radicals (29). However, Vita *et al.* (9) found that long-term statin treatment did not have any significant effect on coronary endothelial vasomotor function in patients with CAD and mildly elevated cholesterol levels. These findings suggest that the effects of lower cholesterol levels on endothelial function are more complex than previously thought in high-risk CAD patients with statin treatment (9).

In the present study, we demonstrated that male MI patients who had been treated with statin therapy for at least 6 months had impaired endothelium-dependent vasodilatation compared to the normal coronary artery and AP groups. We also demonstrated that male MI patients who had been treated with statin had higher levels of Lp(a), glucose and insulin than the other groups. Since these three risk factors have been associated with impaired endothelium-dependent vasodilatation (15, 16, 20, 21), our data may indicate that these risk factors could be involved in impaired endothelial function in male CAD patients on statins. Our findings also may

explain the complexity of impaired endothelial function in high-risk patients after statin therapy (9), and other underlying factors, including Lp(a), glucose or insulin, may affect endothelial function after statin treatment.

Endothelial dysfunction is known to be related to several individual atherosclerotic factors, including aging, smoking and hypertension (10–14). In this study, SBP and DBP were associated with impaired endothelial function, while there were no significant associations of endothelial dysfunction with aging or smoking habit. Although the reason that impaired endothelial function was not significantly associated with aging or smoking habit remains unclear, it is possible that differences in the study populations between the present and previous studies, which have included essential hypertensive subjects and healthy volunteers, respectively, may have influenced the results. We selected angiographically defined normal coronary subjects with hypercholesterolemia as a normal coronary control group. A selection bias is known to exist in terms of control subjects who have undergone coronary angiography: angiographically defined normal subjects generally have more risk factors for CAD compared to patients who show clinical symptoms but who have not been selected for angiography, since a person with both a clinical symptom and a known risk factor, such as smoking, may be more likely to be referred for angiography than a person with a clinical symptom alone. This selection bias regarding control subjects may explain why there was no significant association of FMD with known atherosclerotic factors such as

aging and smoking habit and why the values for endothelium-independent vasodilatation in this study tended to be lower than those in a previous report (18). Thus, limitations regarding the controls may have limited the power of this study.

In contrast to endothelial dysfunction, no significant differences in indices of the severity of coronary atherosclerosis, *i.e.*, number of diseased vessels and coronary score, were observed between the AP and MI groups in this study. These data suggest that the MI group had more advanced endothelial dysfunction than the AP group, while there was no difference in the severity of coronary atherosclerosis between these two groups. Endothelial dysfunction is involved in the progression or severity of atherosclerosis in CAD (4), and MI is the result of atherosclerosis, a vascular disorder characterized by abnormalities in endothelial function, resulting in plaque instability, thrombus formation and complete vessel occlusion (14). Our data, which show a difference in endothelial dysfunction between MI and AP, may explain the difference in clinical cardiac events in MI caused by plaque instability and thrombus formation.

Measurement of Lp(a), glucose and insulin may be useful for evaluating endothelial function in CAD patients on statins. Lp(a) is related to impaired endothelium-dependent dilatation (15, 16) and is also an independent risk factor for atherogenic disease (17–19). Some studies have demonstrated that Lp(a) has effects similar to LDL-C on atherogenesis (30) and that Lp(a) also inactivates nitric oxide through superoxide anion production and interferes with the stimulation of nitric oxide synthase on the endothelium (27). Hyperglycemia and hyperinsulinemia are also involved in the impairment of endothelial function through lower nitric oxide bioavailability *via* the imbalance of nitric oxide and superoxide (20, 21). In this study, the MI group showed significantly lower FMD levels accompanied by higher levels of Lp(a), glucose and insulin, and these risk factors correlated with lower FMD levels as well as SBP and DBP and the status of MI. Lp(a) was also significantly correlated with impaired FMD by a multivariate analysis. These data indicate that, even after receiving statin treatment, endothelial dysfunction was significant in male patients with CAD and that higher levels of Lp(a), glucose and insulin are associated with impaired endothelial function. Since high-risk patients with CAD should be subjected to aggressive risk factor management (31), risk-reduction therapies for endothelial dysfunction may be important in male MI patients. Additional management of higher levels of Lp(a), glucose and insulin might be beneficial for improving endothelial dysfunction in male MI patients.

Angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers, as well as statins, have been shown to have favorable effects on endothelial function in patients with atherosclerosis (12, 14). In this study, although a significantly higher percentage of patients in the MI group were taking angiotensin II type 1 receptor antagonists, compared to the normal coronary artery group, the MI group

showed a lower FMD than the other groups. Although our study had a cross-sectional design, these data may indicate that the impaired endothelial function in male MI patients was resistant to combined treatment with statin and angiotensin II type 1 receptor antagonists. A prospective or crossover study with statin administration in high-risk CAD patients, such as those with MI, may provide more convincing information on the depressed endothelial function in such patients.

In conclusion, even after receiving cholesterol-lowering treatment, male patients with MI showed endothelial dysfunction, and higher levels of Lp(a), glucose and insulin are possible markers for endothelial dysfunction in such patients.

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